PATENTS • DESIGNS • COPYRIGHT • TRADE MARKS
The Patent Office

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

-registration under the Companies Act does not constitute a new legal entity but merely jects the company to certain additional company law rules.

Signed P. Mahoney

Dated 21 November 2003

Form 1/77

Act 1977

THE PATENT OFFICE
A
- 6 NOV 2002
LONDON

The Patent Office

P/77

07NOV02 E761561-1 D02639
P01/7700 0.00-0225923.2

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

Request for grant of a patent

notes on the back of this form. You can also get
natory leaflet from the Patent Office to help
in this form)

Your reference	T1567PV
Patent application number (The Patent Office will fill in this par	0225923.2
	6 NOV 2002
Full name, address and postcode of the or of each applicant (underline all surnames)	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom
Patents ADP number (if you know it)	00597799001 ✓
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
Title of the invention	Therapeutic agents
Name of your agent (if you have one)	Dr. J. Thompson
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	Merck & Co., Inc. European Patent Department Terlings Park Eastwick Road Harlow Essex CM20 2QR
Patents ADP number (if you know it)	4392742002 ✓

If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority Application number (if you know it)	Date of filing (day/month/year)

If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:	Yes

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	32
Claim(s)	0
Abstract	0
Drawing(s)	0

CF

10. If you are also filing any of the following, state how many against each item.

Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	-
Request for preliminary examination and search (Patents Form 9/77)	-
Request for substantive examination (Patents Form 10/77)	-
Any other documents (please specify)	-

11. I/We request the grant of a patent on the basis of this application.

Signature J. Thompson Date 06 November 2002

Dr. J. Thompson

12. Name and daytime telephone number of person to contact in the United Kingdom — Dr. J. Thompson — 01279 440172

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

Write your answers in capital letters using black ink or you may type them.

If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

If you have answered 'Yes' Patents Form 7/77 will need to be filed.

Once you have filled in the form you must remember to sign and date it.

For details of the fee and ways to pay please contact the Patent Office.

THERAPEUTIC AGENTS

The present invention relates to a class of substituted imidazo-pyrazinone derivatives and to their use in therapy. More particularly, this invention is concerned with imidazo[1,2-α]pyrazin-8-one analogues which are substituted in the 3-position by a substituted phenyl ring. These compounds are ligands for $GABA_A$ receptors and are therefore useful in the therapy of deleterious neurological complaints.

Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) $GABA_A$ receptors, which are members of the ligand-gated ion channel superfamily; and (2) $GABA_B$ receptors, which may be members of the G-protein linked receptor superfamily. Since the first cDNAs encoding individual $GABA_A$ receptor subunits were cloned the number of known members of the mammalian family has grown to include at least six α subunits, four β subunits, three γ subunits, one δ subunit, one ε subunit and two ρ subunits.

Although knowledge of the diversity of the $GABA_A$ receptor gene family represents a huge step forward in our understanding of this ligand-gated ion channel, insight into the extent of subtype diversity is still at an early stage. It has been indicated that an α subunit, a β subunit and a γ subunit constitute the minimum requirement for forming a fully functional $GABA_A$ receptor expressed by transiently transfecting cDNAs into cells. As indicated above, δ, ε and ρ subunits also exist, but are present only to a minor extent in $GABA_A$ receptor populations.

Studies of receptor size and visualisation by electron microscopy conclude that, like other members of the ligand-gated ion channel family, the native $GABA_A$ receptor exists in pentameric form. The selection of at least one α, one β and one γ subunit from a repertoire of seventeen allows for the possible existence of more than 10,000 pentameric subunit combinations. Moreover, this calculation overlooks the additional

permutations that would be possible if the arrangement of subunits around the ion channel had no constraints (i.e. there could be 120 possible variants for a receptor composed of five different subunits).

Receptor subtype assemblies which do exist include, amongst many others, $\alpha1\beta2\gamma2$, $\alpha2\beta\gamma1$, $\alpha2\beta2/3\gamma2$, $\alpha3\beta\gamma2/3$, $\alpha4\beta\delta$, $\alpha5\beta3\gamma2/3$, $\alpha6\beta\gamma2$ and $\alpha6\beta\delta$. Subtype assemblies containing an $\alpha1$ subunit are present in most areas of the brain and are thought to account for over 40% of $GABA_A$ receptors in the rat. Subtype assemblies containing $\alpha2$ and $\alpha3$ subunits respectively are thought to account for about 25% and 17% of $GABA_A$ receptors in the rat. Subtype assemblies containing an $\alpha5$ subunit are expressed predominantly in the hippocampus and cortex and are thought to represent about 4% of $GABA_A$ receptors in the rat.

A characteristic property of all known $GABA_A$ receptors is the presence of a number of modulatory sites, one of which is the benzodiazepine (BZ) binding site. The BZ binding site is the most explored of the $GABA_A$ receptor modulatory sites, and is the site through which anxiolytic drugs such as diazepam and temazepam exert their effect. Before the cloning of the $GABA_A$ receptor gene family, the benzodiazepine binding site was historically subdivided into two subtypes, BZ1 and BZ2, on the basis of radioligand binding studies. The BZ1 subtype has been shown to be pharmacologically equivalent to a $GABA_A$ receptor comprising the $\alpha1$ subunit in combination with a β subunit and $\gamma2$. This is the most abundant $GABA_A$ receptor subtype, and is believed to represent almost half of all $GABA_A$ receptors in the brain.

Two other major populations are the $\alpha2\beta\gamma2$ and $\alpha3\beta\gamma2/3$ subtypes. Together these constitute approximately a further 35% of the total $GABA_A$ receptor repertoire. Pharmacologically this combination appears to be equivalent to the BZ2 subtype as defined previously by radioligand binding, although the BZ2 subtype may also include certain $\alpha5$-containing subtype assemblies. The physiological role of these subtypes has hitherto

been unclear because no sufficiently selective agonists or antagonists were known.

It is now believed that agents acting as BZ agonists at $\alpha1\beta\gamma2$, $\alpha2\beta\gamma2$ or $\alpha3\beta\gamma2$ subtypes will possess desirable anxiolytic properties. Compounds which are modulators of the benzodiazepine binding site of the $GABA_A$ receptor by acting as BZ agonists are referred to hereinafter as "$GABA_A$ receptor agonists". The $\alpha1$-selective $GABA_A$ receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through $GABA_A$ receptors containing the $\alpha1$ subunit. Accordingly, it is considered that $GABA_A$ receptor agonists which interact more favourably with the $\alpha2$ and/or $\alpha3$ subunit than with $\alpha1$ will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Moreover, agents which are inverse agonists of the $\alpha5$ subunit are likely to be beneficial in enhancing cognition, for example in subjects suffering from dementing conditions such as Alzheimer's disease. Also, agents which are antagonists or inverse agonists at $\alpha1$ might be employed to reverse sedation or hypnosis caused by $\alpha1$ agonists.

The compounds of the present invention, being selective ligands for $GABA_A$ receptors, are therefore of use in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine; depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder; psychotic disorders including schizophrenia; neurodegeneration arising from cerebral

ischemia; attention deficit hyperactivity disorder; Tourette's syndrome; speech disorders, including stuttering; and disorders of circadian rhythm, e.g. in subjects suffering from the effects of jet lag or shift work.

Further disorders for which selective ligands for $GABA_A$ receptors may be of benefit include pain and nociception; emesis, including acute, delayed and anticipatory emesis, in particular emesis induced by chemotherapy or radiation, as well as motion sickness, and post-operative nausea and vomiting; eating disorders including anorexia nervosa and bulimia nervosa; premenstrual syndrome; muscle spasm or spasticity, e.g. in paraplegic patients; hearing disorders, including tinnitus and age-related hearing impairment; urinary incontinence; and the effects of substance abuse or dependency, including alcohol withdrawal. Selective ligands for $GABA_A$ receptors may be beneficial in enhancing cognition, for example in subjects suffering from dementing conditions such as Alzheimer's disease; and may also be effective as pre-medication prior to anaesthesia or minor procedures such as endoscopy, including gastric endoscopy.

In addition, the compounds in accordance with the present invention may be useful as radioligands in assays for detecting compounds capable of binding to the human $GABA_A$ receptor.

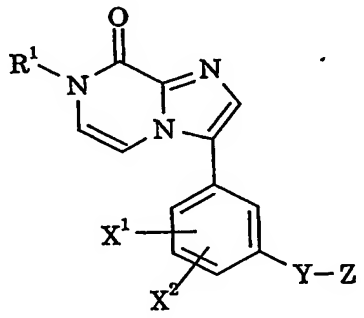
WO 02/10170 describes a class of 3-phenylimidazo[1,2-*a*]pyrazine derivatives which are stated to be selective ligands for $GABA_A$ receptors, in particular having high affinity for the α2 and/or α3 subunit thereof, and accordingly to be of benefit in the treatment and/or prevention of neurological disorders, including anxiety and convulsions. However, there is no disclosure nor any suggestion in that publication of therapeutic agents based on a 7-substituted imidazo[1,2-*a*]pyrazin-8-one ring system.

The present invention provides a class of imidazo-pyrazinone derivatives which possess desirable binding properties at various $GABA_A$ receptor subtypes. The compounds in accordance with the present invention have good affinity as ligands for the α2 and/or α3 and/or α5

subunit of the human $GABA_A$ receptor. The compounds of this invention may interact more favourably with the α2 and/or α3 subunit than with the α1 subunit; and/or may interact more favourably with the α5 subunit than with the α1 subunit.

The compounds of the present invention are $GABA_A$ receptor subtype ligands having a binding affinity (K_i) for the α2 and/or α3 and/or α5 subunit, as measured in the assay described hereinbelow, of 200 nM or less, typically of 100 nM or less, and ideally of 20 nM or less. The compounds in accordance with this invention may possess at least a 2-fold, suitably at least a 5-fold, and advantageously at least a 10-fold, selective affinity for the α2 and/or α3 and/or α5 subunit relative to the α1 subunit. However, compounds which are not selective in terms of their binding affinity for the α2 and/or α3 and/or α5 subunit relative to the α1 subunit are also encompassed within the scope of the present invention; such compounds will desirably exhibit functional selectivity in terms of zero or weak (positive or negative) efficacy at the α1 subunit and (i) a full or partial agonist profile at the α2 and/or α3 subunit, and/or (ii) an inverse agonist profile at the α5 subunit.

The present invention provides a compound of formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein

X^1 represents hydrogen, halogen, C_{1-6} alkyl, trifluoromethyl or C_{1-6} alkoxy;

X^2 represents hydrogen or halogen;

Y represents a chemical bond, an oxygen atom, or a -NH- linkage;

Z represents an optionally substituted aryl or heteroaryl group;

R^1 represents hydrocarbon, a heterocyclic group, trifluoromethyl, $-SO_2R^a$, $-SO_2NR^aR^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$; and

R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.

The aryl or heteroaryl group Z in the compounds of formula I above may be unsubstituted, or substituted by one or more substituents. Typically, the group Z will be unsubstituted, or substituted by one or two substituents. Suitably, the group Z is unsubstituted or monosubstituted. Typical substituents on the group Z include halogen, cyano, nitro, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, oxy, C_{1-6} alkylsulphonyl, amino, aminocarbonyl, formyl, C_{2-6} alkoxycarbonyl and $-CR^a=NOR^b$, wherein R^a and R^b are as defined above.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal

salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, indanyl, aryl and aryl(C_{1-6})alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl and heteroaryl(C_{1-6})alkyl groups.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *tert*-butyl and 2,2-dimethylpropyl. Derived expressions such as "C_{1-6} alkoxy", "C_{1-6} alkylamino" and "C_{1-6} alkylsulphonyl" are to be construed accordingly.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl and dimethylallyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

Typical examples of C_{3-7} cycloalkyl(C_{1-6})alkyl groups include cyclopropylmethyl, cyclohexylmethyl and cyclohexylethyl.

Particular indanyl groups include indan-1-yl and indan-2-yl.

Particular aryl groups include phenyl and naphthyl, preferably phenyl.

Particular aryl(C_{1-6})alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl groups.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The expression "heteroaryl(C_{1-6})alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, oxazolylmethyl, oxazolylethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl and isoquinolinylmethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C_{1-6} alkyl, adamantyl, phenyl, halogen, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, aryloxy, keto, C_{1-3} alkylenedioxy, nitro, cyano, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkoxycarbonyl(C_{1-6})alkyl, C_{2-6} alkylcarbonyloxy, arylcarbonyloxy, aminocarbonyloxy, C_{2-6} alkylcarbonyl, arylcarbonyl, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, arylsulphonyl, $-NR^vR^w$, $-NR^vCOR^w$, $-NR^vCO_2R^w$, $-NR^vSO_2R^w$, $-CH_2NR^vSO_2R^w$, $-NHCONR^vR^w$, $-CONR^vR^w$, $-SO_2NR^vR^w$ and $-CH_2SO_2NR^vR^w$, in which R^v and R^w independently represent hydrogen, C_{1-6} alkyl, aryl or aryl(C_{1-6})alkyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluoro or chloro.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Suitable values for the X^1 substituent include hydrogen, fluoro, chloro, methyl, trifluoromethyl and methoxy; in particular hydrogen or fluoro; and especially fluoro.

Suitably, X^1 represents halogen, C_{1-6} alkyl, trifluoromethyl or C_{1-6} alkoxy. Typical values of X^1 include fluoro, chloro, methyl, trifluoromethyl and methoxy, especially fluoro.

Typical values of X^2 include hydrogen and fluoro, especially hydrogen.

In a preferred embodiment, Y represents a chemical bond.

In another embodiment, Y represents an oxygen atom.

In a further embodiment, Y represents a -NH- linkage.

Selected values for the substituent Z include phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl, any of which groups may be optionally substituted by one or more substituents.

In one favoured embodiment, Z represents an optionally substituted phenyl group, in particular monosubstituted or disubstituted phenyl. In another favoured embodiment, Z represents optionally substituted pyridinyl, especially unsubstituted, monosubstituted or disubstituted pyridin-2-yl, pyridin-3-yl or pyridin-4-yl.

Examples of suitable substituents on the group Z include fluoro, chloro, cyano, nitro, methyl, hydroxy, methoxy, oxy, methanesulphonyl, amino, aminocarbonyl, formyl, methoxycarbonyl and -CH=NOH.

Examples of particular substituents on the group Z include fluoro and cyano, especially cyano.

Detailed values of Z include cyanophenyl, (cyano)(fluoro)phenyl, (chloro)(cyano)phenyl, nitrophenyl, methoxyphenyl, methanesulphonyl-phenyl, pyridinyl, fluoro-pyridinyl, difluoro-pyridinyl, (amino)(chloro)pyridinyl, cyano-pyridinyl, methyl-pyridinyl, hydroxy-pyridinyl, methoxy-pyridinyl, oxy-pyridinyl, aminocarbonyl-pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, cyano-thienyl, aminocarbonyl-thienyl, formyl-thienyl, methoxycarbonyl-thienyl, thienyl-CH=NOH, thiazolyl, isothiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl and methyl-tetrazolyl.

Specific values of Z include cyanophenyl, (cyano)(fluoro)phenyl, pyridinyl, difluoro-pyridinyl and cyano-pyridinyl.

In one embodiment, Z represents cyanophenyl, especially 2-cyanophenyl.

In another embodiment, Z represents (cyano)(fluoro)phenyl, especially 2-cyano-4-fluorophenyl.

Typically, R^1 represents hydrocarbon, a heterocyclic group, trifluoromethyl, $-COR^a$ or $-CO_2R^a$.

Typical values of R^a include hydrogen and C_{1-6} alkyl. Suitably, R^a represents hydrogen or methyl.

Typical values of R^b include hydrogen, C_{1-6} alkyl, hydroxy(C_{1-6})alkyl and di(C_{1-6})alkylamino(C_{1-6})alkyl. Suitably, R^b represents hydrogen, methyl, ethyl, hydroxyethyl or dimethylaminoethyl. Particular values of R^b include hydrogen, hydroxyethyl and dimethylaminoethyl, especially hydrogen or dimethylaminoethyl.

Suitable values of R^1 include C_{1-6} alkyl, halo(C_{1-6})alkyl, dihalo(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, dihydroxy(C_{1-6})alkyl, C_{1-6} alkoxy(C_{1-6})alkyl, di(C_{1-6})alkoxy(C_{1-6})alkyl, cyano(C_{1-6})alkyl, C_{2-6} alkoxycarbonyl(C_{1-6})alkyl, C_{3-7} cycloalkyl, heteroaryl, C_{1-6} alkyl-heteroaryl,

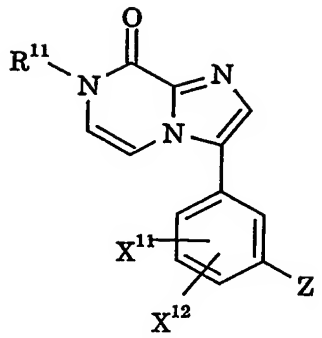
heteroaryl(C_{1-6})alkyl, trifluoromethyl, formyl, C_{2-6} alkylcarbonyl and C_{2-6} alkoxycarbonyl.

Representative values of R^1 include C_{1-6} alkyl, halo(C_{1-6})alkyl, dihalo(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl and trifluoromethyl.

Individual values of R^1 include methyl, ethyl, fluoromethyl, difluoromethyl, hydroxymethyl, methoxymethyl, dimethoxymethyl, hydroxyethyl (especially 2-hydroxyethyl), fluoroethyl (especially 2-fluoroethyl), difluoroethyl (especially 2,2-difluoroethyl), dimethoxyethyl (especially 2,2-dimethoxyethyl), isopropyl, hydroxypropyl (especially 2-hydroxyprop-2-yl), dihydroxypropyl (especially 1,2-dihydroxyprop-2-yl), fluoropropyl (especially 2-fluoroprop-2-yl), cyanopropyl (especially 2-cyanoprop-2-yl), methoxycarbonylpropyl (especially 2-methoxycarbonylprop-2-yl), *tert*-butyl, hydroxybutyl (especially 1-hydroxy-2-methylprop-2-yl), cyclopropyl, pyridinyl, furyl, thienyl, oxazolyl, methylthiazolyl, methyloxadiazolyl, imidazolylmethyl, triazolylmethyl, trifluoromethyl, formyl, acetyl and methoxycarbonyl.

In a first embodiment, R^1 represents methyl. In a second embodiment, R^1 represents ethyl. In a third embodiment, R^1 represents fluoroethyl (especially 2-fluoroethyl). In a fourth embodiment, R^1 represents difluoroethyl (especially 2,2-difluoroethyl). In a favoured embodiment, R^1 represents 2-hydroxyprop-2-yl. In another embodiment, R^1 represents 2-fluoroprop-2-yl. In an additional embodiment, R^1 represents trifluoromethyl.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and pharmaceutically acceptable salts thereof:



(IIA)

wherein

Z is as defined above;

X^{11} represents hydrogen, fluoro, chloro, methyl, trifluoromethyl or methoxy;

X^{12} represents hydrogen or fluoro; and

R^{11} represents C_{1-6} alkyl, halo(C_{1-6})alkyl, dihalo(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, dihydroxy(C_{1-6})alkyl, C_{1-6} alkoxy(C_{1-6})alkyl, di(C_{1-6})alkoxy(C_{1-6})alkyl, cyano(C_{1-6})alkyl, C_{2-6} alkoxycarbonyl(C_{1-6})alkyl, C_{3-7} cycloalkyl, heteroaryl, C_{1-6} alkyl-heteroaryl, heteroaryl(C_{1-6})alkyl, trifluoromethyl, formyl, C_{2-6} alkylcarbonyl or C_{2-6} alkoxycarbonyl.

Suitable values of X^{11} include hydrogen and fluoro, especially fluoro.

Typical values of X^{11} include fluoro, chloro, methyl, trifluoromethyl and methoxy.

A particular value of X^{11} is fluoro.

In a favoured embodiment, X^{12} represents hydrogen. In another embodiment, X^{12} represents fluoro.

Where R^{11} represents heteroaryl, this group is suitably pyridinyl, furyl, thienyl or oxazolyl.

Where R^{11} represents C_{1-6} alkyl-heteroaryl, this group is suitably methylthiazolyl (e.g. 2-methylthiazol-5-yl) or methyloxadiazolyl (e.g. 3-methyl-[1,2,4]oxadiazol-5-yl).

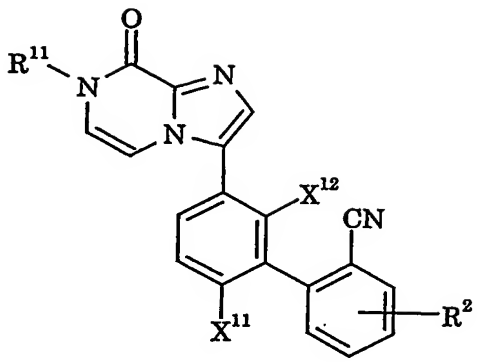
Where R^{11} represents heteroaryl(C_{1-6})alkyl, this group is suitably imidazolylmethyl or triazolylmethyl.

Representative values of R^{11} include C_{1-6} alkyl, halo(C_{1-6})alkyl, dihalo(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl and trifluoromethyl.

Individual values of R^{11} include methyl, ethyl, fluoromethyl, difluoromethyl, hydroxymethyl, methoxymethyl, dimethoxymethyl, hydroxyethyl (especially 2-hydroxyethyl), fluoroethyl (especially 2-fluoroethyl), difluoroethyl (especially 2,2-difluoroethyl), dimethoxyethyl (especially 2,2-dimethoxyethyl), isopropyl, hydroxypropyl (especially 2-hydroxyprop-2-yl), dihydroxypropyl (especially 1,2-dihydroxyprop-2-yl), fluoropropyl (especially 2-fluoroprop-2-yl), cyanopropyl (especially 2-cyanoprop-2-yl), methoxycarbonylpropyl (especially 2-methoxycarbonylprop-2-yl), *tert*-butyl, hydroxybutyl (especially 1-hydroxy-2-methylprop-2-yl), cyclopropyl, pyridinyl, furyl, thienyl, oxazolyl, methylthiazolyl, methyloxadiazolyl, imidazolylmethyl, triazolylmethyl, trifluoromethyl, formyl, acetyl and methoxycarbonyl.

In a first embodiment, R^{11} represents methyl. In a second embodiment, R^{11} represents ethyl. In a third embodiment, R^{11} represents fluoroethyl (especially 2-fluoroethyl). In a fourth embodiment, R^{11} represents difluoroethyl (especially 2,2-difluoroethyl). In a favoured embodiment, R^{11} represents 2-hydroxyprop-2-yl. In another embodiment, R^{11} represents 2-fluoroprop-2-yl. In an additional embodiment, R^{11} represents trifluoromethyl.

One representative subset of the compounds of formula IIA above is represented by the compounds of formula IIB, and pharmaceutically acceptable salts thereof:



(IIB)

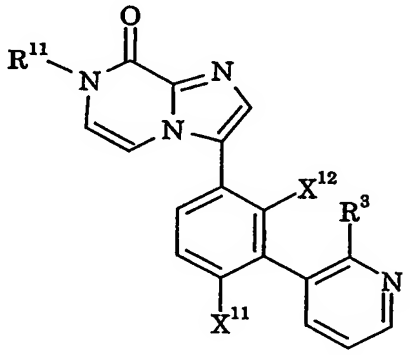
wherein X^{11}, X^{12} and R^{11} are as defined above; and

R^2 represents hydrogen or fluoro.

In one embodiment, R^2 is hydrogen.

In another embodiment, R^2 is fluoro, in which case the fluorine atom R^2 is favourably attached to the phenyl ring at the 4-, 5- or 6-position (relative to the cyano group at position 2).

Another representative subset of the compounds of formula IIA above is represented by the compounds of formula IIC, and pharmaceutically acceptable salts thereof:



(IIC)

wherein X^{11}, X^{12} and R^{11} are as defined above; and

R^3 represents hydrogen, fluoro, cyano or methyl.

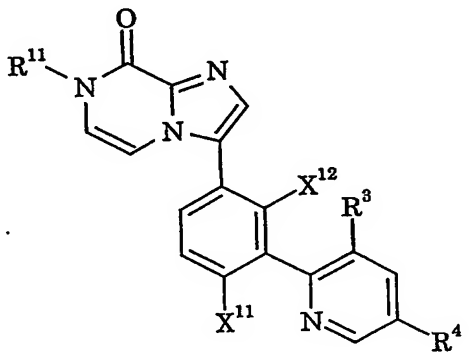
In one embodiment, R^3 is hydrogen.

In an additional embodiment, R^3 is fluoro.

In another embodiment, R^3 is cyano.

In a further embodiment, R^3 is methyl.

A further representative subset of the compounds of formula IIA above is represented by the compounds of formula IID, and pharmaceutically acceptable salts thereof:



(IID)

wherein X^{11}, X^{12}, R^3 and R^{11} are as defined above; and

R^4 represents hydrogen or fluoro.

Suitably, R^4 represents hydrogen.

In another embodiment, R^4 represents fluoro.

Specific compounds within the scope of the present invention include:

2′-fluoro-5′-(7-methyl-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl)-biphenyl-2-carbonitrile;

5′-(7-ethyl-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl)-2′-fluorobiphenyl-2-carbonitrile;

2′-fluoro-5′-[7-(2-fluoroethyl)-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl]biphenyl-2-carbonitrile;

5'-[7-(2,2-difluoroethyl)-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl]-2'-fluorobiphenyl-2-carbonitrile;

4,2'-difluoro-5'-(7-methyl-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl)-biphenyl-2-carbonitrile;

and pharmaceutically acceptable salts thereof.

Also provided by the present invention is a method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof.

Further provided by the present invention is a method for the treatment and/or prevention of convulsions (e.g. in a patient suffering from epilepsy or a related disorder) which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof.

The binding affinity (K_i) of the compounds according to the present invention for the α3 subunit of the human $GABA_A$ receptor is conveniently as measured in the assay described hereinbelow. The α3 subunit binding affinity (K_i) of the anxiolytic compounds of the invention is ideally 50 nM or less, preferably 10 nM or less, and more preferably 5 nM or less.

The anxiolytic compounds according to the present invention will ideally elicit at least a 40%, preferably at least a 50%, and more preferably at least a 60%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor. Moreover, the compounds of the invention will ideally elicit at most a 30%, preferably at most a 20%, and more preferably at most a 10%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α1 subunit of the human $GABA_A$ receptor.

The potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α3 and α1 subunits of the human $GABA_A$ receptor can conveniently be measured by procedures analogous to the protocol

described in Wafford *et al.*, *Mol. Pharmacol.*, 1996, **50**, 670-678. The procedure will suitably be carried out utilising cultures of stably transfected eukaryotic cells, typically of stably transfected mouse Ltk- fibroblast cells.

The compounds according to the present invention may exhibit anxiolytic activity, as may be demonstrated by a positive response in the elevated plus maze and conditioned suppression of drinking tests (cf. Dawson *et al.*, *Psychopharmacology*, 1995, **121**, 109-117). Moreover, the compounds of the invention are likely to be substantially non-sedating, as may be confirmed by an appropriate result obtained from the response sensitivity (chain-pulling) test (cf. Bayley *et al.*, *J. Psychopharmacol.*, 1996, **10**, 206-213).

The compounds according to the present invention may also exhibit anticonvulsant activity. This can be demonstrated by the ability to block pentylenetetrazole-induced seizures in rats and mice, following a protocol analogous to that described by Bristow *et al.* in *J. Pharmacol. Exp. Ther.*, 1996, **279**, 492-501.

In another aspect, the present invention provides a method for the treatment and/or prevention of cognitive disorders, including dementing conditions such as Alzheimer's disease, which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof.

Cognition enhancement can be shown by testing the compounds in the Morris watermaze as reported by McNamara and Skelton, *Psychobiology*, 1993, **21**, 101-108. Further details of relevant methodology are described in WO 96/25948.

Cognitive disorders for which the compounds of the present invention may be of benefit include delirium, dementia, amnestic disorders, and cognition deficits, including age-related memory deficits, due to traumatic injury, stroke, Parkinson's disease and Down Syndrome. Any of these conditions may be attributable to substance abuse or

withdrawal. Examples of dementia include dementia of the Alzheimer's type with early or late onset, and vascular dementia, any of which may be uncomplicated or accompanied by delirium, delusions or depressed mood; and dementia due to HIV disease, head trauma, Parkinson's disease or Creutzfeld-Jakob disease.

In order to elicit their behavioural effects, the compounds of the invention will ideally be brain-penetrant; in other words, these compounds will be capable of crossing the so-called "blood-brain barrier". Preferably, the compounds of the invention will be capable of exerting their beneficial therapeutic action following administration by the oral route.

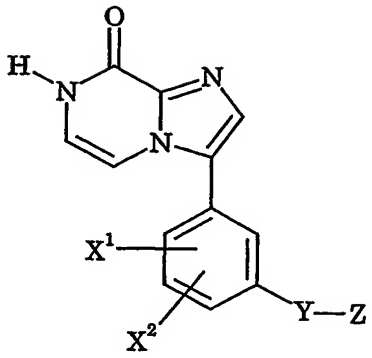
The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the

present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of neurological disorders, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds in accordance with the present invention may be prepared by a process which comprises attachment of the R^1 moiety to a compound of formula III:



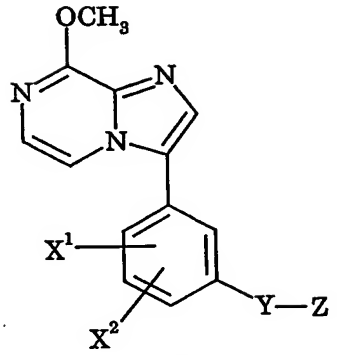
(III)

wherein X^1, X^2, Y and Z are as defined above; by conventional alkylation or acylation methods.

For instance, where R^1 in the compounds of formula I above represents an optionally substituted C_{1-6} alkyl group, the moiety R^1 may be attached by treating the appropriate compound of formula III with a suitable alkyl halide, e.g. iodomethane, iodoethane, 1-bromo-2-fluoroethane or 2-bromo-1,1-difluoroethane, typically in the presence of a base such as sodium hydride. Alternatively, where R^1 in the compounds of formula I above represents methyl, the methyl group R^1 may be attached by treating the appropriate compound of formula III with a strong base such as hexamethyldisilazane, followed by chloro(chloromethyl)-dimethylsilane; and subsequently treating the compound thereby obtained with cesium fluoride.

Except where X^1 and X^2 both simultaneously represent hydrogen, the compounds of formula III above are novel compounds and represent a further feature of the present invention.

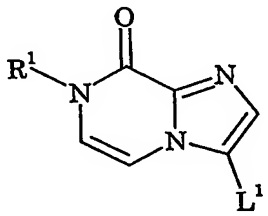
The compounds of formula III may suitably be prepared from the appropriate methoxy-substituted compound of formula IV:



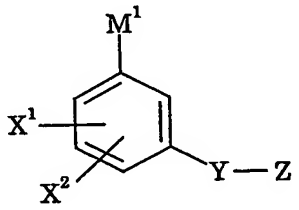
(IV)

wherein X^1, X^2, Y and Z are as defined above; by treatment with hydrogen bromide, typically in acetic acid.

In another procedure, the compounds in accordance with the present invention may be prepared by a process which comprises reacting a compound of formula V with a compound of formula VI:



(V)



(VI)

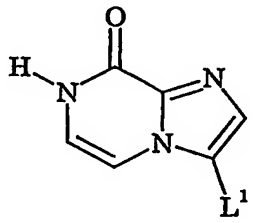
wherein X^1, X^2, Y, Z and R^1 are as defined above, L^1 represents a suitable leaving group, and M^1 represents a boronic acid moiety $-B(OH)_2$ or a cyclic ester thereof formed with an organic diol, e.g. pinacol, 1,3-propanediol or neopentyl glycol, or M^1 represents $-Sn(Alk)_3$ in which Alk represents a C_{1-6} alkyl group, typically *n*-butyl; in the presence of a transition metal catalyst.

The leaving group L^1 is typically a halogen atom, e.g. bromo.

The transition metal catalyst of use in the reaction between compounds V and VI is suitably palladium(II) acetate, in which case the reaction is typically accomplished in the presence of triphenylphosphine.

The reaction is conveniently carried out at an elevated temperature in a solvent such as 1,4-dioxane, typically in the presence of sodium carbonate.

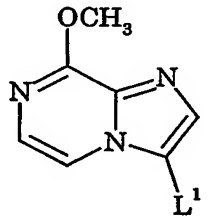
The intermediates of formula V may be prepared by attaching the R^1 moiety to a compound of formula VII:



(VII)

wherein L^1 is as defined above; under conditions analogous to those described above for attachment of the R^1 moiety to a compound of formula III.

The intermediates of formula VII may be prepared from the appropriate methoxy-substituted precursor of formula VIII:



(VIII)

wherein L^1 is as defined above; by treatment with hydrogen bromide, typically in acetic acid.

The compounds of formula IV, VI and VIII may conveniently be prepared by the procedures described in WO 02/10170, or by methods analogous thereto.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate,

subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I wherein R^1 represents $-C(O\text{-}Alk^1)_2R^a$ initially obtained, wherein Alk^1 is C_{1-6} alkyl, typically methyl or ethyl, may be converted into the corresponding compound of formula I wherein R^1 represents $-COR^a$ by hydrolysis with a mineral acid, typically aqueous hydrochloric acid. A compound wherein R^1 represents formyl may be reduced with sodium triacetoxyborohydride to the corresponding compound wherein R^1 represents hydroxymethyl. A compound of formula I wherein R^1 represents C_{2-6} alkoxycarbonyl may be reduced with lithium aluminium hydride to the corresponding compound of formula I wherein R^1 represents hydroxymethyl. A compound of formula I wherein R^1 represents hydroxymethyl may be oxidised to the corresponding compound of formula I wherein R^1 represents formyl by treatment with manganese dioxide. Alternatively, the compound of formula I wherein R^1 represents formyl may be reacted with a Grignard reagent of formula R^aMgBr to afford a compound of formula I wherein R^1 represents $-CH(OH)R^a$, and this compound may in turn be oxidised using manganese dioxide to the corresponding compound of formula I wherein R^1 represents $-COR^a$. A compound of formula I wherein R^1 represents $-CH(OH)R^a$ may be converted into the corresponding compound of formula I wherein R^1 represents $-CHFR^a$ by treatment with (diethylamino)sulfur trifluoride (DAST). Similarly, a compound of formula I wherein R^1 represents $-COR^a$ may be converted into the corresponding compound of formula I wherein R^1 represents $-CF_2R^a$ by treatment with DAST. A compound of formula I wherein R^1 represents $-COCH_3$ may be treated with thioacetamide in the presence of pyridinium tribromide to furnish the corresponding compound of formula I wherein R^1 represents 2-methylthiazol-5-yl. Moreover, a compound of formula I wherein R^1 is formyl may be treated with (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) in the presence of potassium carbonate to afford the corresponding compound of formula I wherein R^1

represents oxazol-5-yl. A compound of formula I wherein R^1 represents hydroxymethyl may be treated with carbon tetrabromide and triphenylphosphine to afford the corresponding compound of formula I wherein R^1 represents bromomethyl, which may then be reacted (typically *in situ*) with the sodium salt of imidazole or 1*H*-[1,2,4]triazole to provide a compound of formula I wherein R^1 represents imidazol-1-ylmethyl or [1,2,4]triazol-1-ylmethyl respectively; or with the sodium salt of 1*H*-[1,2,3]triazole to provide a mixture of compounds of formula I wherein R^1 represents [1,2,3]triazol-1-ylmethyl and [1,2,3]triazol-2-ylmethyl; or with morpholine to provide a compound of formula I wherein R^1 represents morpholin-4-ylmethyl. A compound of formula I wherein Z is substituted with methoxy may be converted to the corresponding compound wherein Z is substituted with hydroxy by treatment with boron tribromide.

Where a mixture of products is obtained from any of the processes described above for the preparation of compounds according to the invention, the desired product can be separated therefrom at an appropriate stage by conventional methods such as preparative HPLC; or column chromatography utilising, for example, silica and/or alumina in conjunction with an appropriate solvent system.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-d-tartaric acid and/or (+)-di-*p*-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric

esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with this invention potently inhibit the binding of [^{3}H]-flumazenil to the benzodiazepine binding site of human $GABA_A$ receptors containing the α2 and/or α3 and/or α5 subunit stably expressed in Ltk$^-$ cells.

Reagents

- Phosphate buffered saline (PBS).
- Assay buffer: 10 mM KH_2PO_4, 100 mM KCl, pH 7.4 at room temperature.
- [^{3}H]-Flumazenil (18 nM for α1β3γ2 cells; 18 nM for α2β3γ2 cells; 10 nM for α3β3γ2 cells; 10 nM for α5β3γ2 cells) in assay buffer.
- Flunitrazepam 100 μM in assay buffer.
- Cells resuspended in assay buffer (1 tray to 10 ml).

Harvesting Cells

Supernatant is removed from cells. PBS (approximately 20 ml) is added. The cells are scraped and placed in a 50 ml centrifuge tube. The procedure is repeated with a further 10 ml of PBS to ensure that most of the cells are removed. The cells are pelleted by centrifuging for 20 min at

3000 rpm in a benchtop centrifuge, and then frozen if desired. The pellets are resuspended in 10 ml of buffer per tray (25 cm x 25 cm) of cells.

Assay

Can be carried out in deep 96-well plates or in tubes. Each tube contains:

- 300 µl of assay buffer.
- 50 µl of [^{3}H]-flumazenil (final concentration for $\alpha1\beta3\gamma2$: 1.8 nM; for $\alpha2\beta3\gamma2$: 1.8 nM; for $\alpha3\beta3\gamma2$: 1.0 nM; for $\alpha5\beta3\gamma2$: 1.0 nM).
- 50 µl of buffer or solvent carrier (e.g. 10% DMSO) if compounds are dissolved in 10% DMSO (total); test compound or flunitrazepam (to determine non-specific binding), 10 µM final concentration.
- 100 µl of cells.

Assays are incubated for 1 hour at 40°C, then filtered using either a Tomtec or Brandel cell harvester onto GF/B filters followed by 3 x 3 ml washes with ice cold assay buffer. Filters are dried and counted by liquid scintillation counting. Expected values for total binding are 3000-4000 dpm for total counts and less than 200 dpm for non-specific binding if using liquid scintillation counting, or 1500-2000 dpm for total counts and less than 200 dpm for non-specific binding if counting with meltilex solid scintillant. Binding parameters are determined by non-linear least squares regression analysis, from which the inhibition constant K_i can be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K_i value for displacement of [^{3}H]-flumazenil from the $\alpha2$ and/or $\alpha3$ and/or $\alpha5$ subunit of the human $GABA_A$ receptor of 100 nM or less.

EXAMPLE 1

2'-Fluoro-5'-(7-methyl-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl)-biphenyl-2-carbonitrile

A suspension of 2,3-dichloropyrazine (35 g, 0.23 mol) in 25% aqueous ammonia (200 ml) was heated at 100°C for 12 h in a PTFE-lined pressure reactor (terminal pressure 100 psi). The reaction was cooled to ambient temperature and the resulting crystalline solid collected by filtration. This solid was triturated with water (150 ml) and dried to afford 2-amino-3-chloropyrazine as a buff-coloured crystalline solid (28 g, 92%): δ_H (400 MHz, DMSO) 6.78 (2H, br s), 7.56 (1H, d, *J* 2.5), 7.95 (1H, d, *J* 2.5).

Bromoacetaldehyde diethyl acetal (45 ml, 0.29 mol) was treated with water (33 ml) and 48% hydrobromic acid (33 ml) and this mixture was heated at 95°C for 90 min. The reaction was cooled, diluted with propan-2-ol (300 ml) and treated with sodium hydrogencarbonate (33 g) added in portions. This mixture was stirred for 30 min then filtered. The filtrate was treated with 2-amino-3-chloropyrazine (25 g, 0.19 mol) and then heated at 90°C for 16 h. The reaction was cooled to ambient temperature, concentrated to about one-third volume and then treated with 48% hydrobromic acid (25 ml). More propan-2-ol (300 ml) was added and the mixture aged for 1 h. The resulting solid was collected by filtration, washed with propan-2-ol and then dissolved in water (500 ml). This solution was made basic by adding solid sodium hydrogencarbonate and then extracted with chloroform (3 x 250 ml). The organics were combined, dried over anhydrous magnesium sulphate, filtered and concentrated to give a solid. Trituration with diethyl ether afforded 8-chloroimidazo[1,2-*a*]pyrazine as an off-white solid (18.6 g, 63%): δ_H (360 MHz, DMSO) 7.73 (1H, d, *J* 4.5), 7.87 (1H, d, *J* 1), 8.28 (1H, d, *J* 1), 8.67 (1H, d, *J* 4.5).

A cooled (0°C) suspension of 8-chloroimidazo[1,2-*a*]pyrazine (18.6 g, 0.12 mol) and sodium acetate (29.8 g, 0.36 mol) in methanol (125 ml, pre-saturated with solid potassium bromide) was treated with bromine (6.5 ml, 0.13 mol) added dropwise over 5 min. After stirring for 10 min thin-layer chromatography indicated no starting material. Solid sodium sulphite (15.3 g, 0.12 mol) was then added to the slurry and stirring continued for 10 min. The mixture was then treated with saturated aqueous sodium hydrogencarbonate (650 ml) added in portions. This mixture was extracted with dichloromethane (2 x 350 ml). The organics were combined, dried over anhydrous magnesium sulphate, filtered and concentrated to afford 3-bromo-8-chloroimidazo[1,2-*a*]pyrazine as a cream-coloured solid: δ_H (400 MHz, $CDCl_3$) 7.82 (1H, d, *J* 4.5), 7.83 (1H, s), 8.05 (1H, d, *J* 4.5). This solid was suspended in 1:1 dichloromethane/methanol (150 ml) and treated with solid sodium methoxide (9.8 g, 0.18 mol). The resulting mixture was then stirred at 40°C for 2 h. The reaction was cooled, diluted with water (750 ml) then extracted with dichloromethane (600 ml). The organics were dried over anhydrous magnesium sulphate, filtered and concentrated to give 3-bromo-8-methoxyimidazo[1,2-*a*]pyrazine as a white solid (24.5 g, 89% over 2 steps): δ_H (360 MHz, DMSO) 4.06 (3H, s), 7.57 (1H, d, *J* 4.5), 7.81 (1H, s), 8.03 (1H, d, *J* 4.5).

A mixture of 3-bromo-8-methoxyimidazo[1,2-*a*]pyrazine (680 mg, 3 mmol) and 2′-fluoro-5′-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-2-carbonitrile (prepared as described in WO 02/074773) (1.45 g, 4.5 mmol) in tetrahydrofuran (9 ml) was treated with 2M sodium carbonate (3 ml) then degassed with nitrogen for 10 min. Tetrakis(triphenylphosphine)palladium(0) (100 mg, 0.09 mmol) was added and this mixture was heated under reflux for 12 h. The reaction was cooled and the majority of the solvent removed on a rotary evaporator. The residue was partitioned between dichloromethane and water. The organics were washed with water, brine, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. Purification of the residue by

chromatography on silica gel eluting with 2% methanol in dichloromethane gave 2′-fluoro-5′-(8-methoxyimidazo[1,2-*a*]pyrazin-3-yl)-biphenyl-2-carbonitrile as a cream solid (768 mg, 74%): δ_H (400 MHz, $CDCl_3$) 4.19 (3H, s), 7.38-7.46 (2H, m), 7.53-7.64 (4H, m), 7.71 (1H, td, *J* 8 and 1.5), 7.73 (1H, s), 7.85 (1H, dd, *J* 8 and 1), 8.02 (1H, d, *J* 4.5); *m/z* (ES$^+$) 345 $[M+H]^+$.

A suspension of 2′-fluoro-5′-(8-methoxyimidazo[1,2-*a*]pyrazin-3-yl)-biphenyl-2-carbonitrile (750 mg, 2.2 mmol) in hydrogen bromide (30 wt % in acetic acid, 10 ml) was heated at 95°C for 45 min. The reaction was cooled, poured into ice water and neutralised by the addition of solid sodium hydrogencarbonate. The resulting solid was collected by filtration and air-dried, then triturated with ether, to afford 2′-fluoro-5′-(8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl)biphenyl-2-carbonitrile as a cream-coloured solid (550 mg, 76%): δ_H (360 MHz, DMSO) 6.92 (1H, t, *J* 6), 7.49 (1H, d, *J* 5), 7.60-7.71 (2H, m), 7.75-7.89 (5H, m), 8.03 (1H, dd, *J* 7 and 0.5), 11.38 (1H, d, *J* 5.5); *m/z* (ES$^+$) 331 $[M+H]^+$.

A suspension of 2′-fluoro-5′-(8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl)biphenyl-2-carbonitrile (250 mg, 0.75 mmol) in acetonitrile (10 ml) was treated with 1,1,1,3,3,3-hexamethyldisilazane (90 µl, 0.41 mmol) and then heated at reflux for 2 h. The resulting gel-like mixture was diluted with acetonitrile (5 ml) then treated with chloro(chloromethyl)-dimethylsilane (110 µl, 0.83 mmol) and heating at reflux continued for 24 h. The reaction was cooled, the acetonitrile removed *in vacuo* and the residue treated with 1,2-dimethoxyethane (12 ml). Caesium fluoride (160 mg, 1.4 mmol) was then added and the reaction heated at reflux for 6 h. After cooling to ambient temperature the mixture was dissolved in 1:1 dichloromethane/methanol and pre-adsorbed onto silica. Purification by chromatography on silica eluting with 4% methanol in dichloromethane (containing 0.5% ammonia) followed by 8% methanol in dichloromethane (containing 0.5% ammonia) gave 2′-fluoro-5′-(7-methyl-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl)biphenyl-2-carbonitrile as a cream-

coloured solid (65 mg, 25%): δ_H (400 MHz, DMSO) 3.47 (3H, s), 7.19 (1H, d, *J* 6), 7.57-7.88 (8H, m), 8.04 (1H, dd, *J* 8 and 1); *m/z* (ES^+) 345 $[M+H]^+$.

EXAMPLE 2

5'-(7-Ethyl-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl)-2'-fluorobiphenyl-2-carbonitrile

A suspension of 2'-fluoro-5'-(8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl)biphenyl-2-carbonitrile (50.0 mg, 0.51 mmol) in 1,2-dimethoxyethane (2 ml) and *N*,*N*-dimethylformamide (0.5 ml) was treated with sodium hydride (6.4 mg of a 60% dispersion in mineral oil, 0.16 mmol). After stirring at ambient temperature for 10 min, lithium bromide (26.3 mg, 0.30 mmol) was added, and stirring continued for 15 min. Iodoethane (24.2 µl, 0.30 mmol) was added and the solution heated at 65°C for 18 h. Water (15 ml) was added and the resulting mixture was extracted with dichloromethane (3 x 10 ml). The combined organic layers were washed with water (10 ml), saturated sodium chloride solution (10 ml), dried over anhydrous magnesium sulphate then concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 2% methanol in dichloromethane. Crystallisation from methanol afforded 5'-(7-ethyl-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl)-2'-fluorobiphenyl-2-carbonitrile as a white solid (23.9 mg, 44%): δ_H (500 MHz, $CDCl_3$) 1.38 (3H, t, *J* 7.2), 4.06 (2H, q, *J* 7.2), 6.72 (1H, d, *J* 5.9), 7.39 (1H, t, *J* 9.3), 7.44 (1H, d, *J* 5.9), 7.53-7.61 (5H, m), 7.69-7.73 (1H, m), 7.84 (1H, d, *J* 7.3); *m/z* (ES^+) 359 $[M+H]^+$.

EXAMPLE 3

2'-Fluoro-5'-[7-(2-fluoroethyl)-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl]biphenyl-2-carbonitrile

The title compound was prepared in the same way as described in Example 2, using 1-bromo-2-fluoroethane instead of iodoethane: δ_H (500 MHz, $CDCl_3$) 4.27 (1H, t, *J* 4.5), 4.32 (1H, t, *J* 4.5), 4.71 (1H, t, *J* 4.4), 4.81 (1H, t, *J* 4.5), 6.80 (1H, d, *J* 5.9), 7.40-7.43 (2H, m), 7.53-7.61 (4H, m), 7.63 (1H, s), 7.69-7.73 (1H, m), 7.85 (1H, d, *J* 7.7); *m/z* (ES^+) 377 $[M+H]^+$.

EXAMPLE 4

5'-[7-(2,2-Difluoroethyl)-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl]-2'-fluorobiphenyl-2-carbonitrile

The title compound was prepared using the method described in Example 2, using 2-bromo-1,1-difluoroethane instead of iodoethane: δ_H (500 MHz, $CDCl_3$) 4.31 (2H, td, *J* 13 and 4.4), 6.14 (1H, tt, *J* 56 and 4.4), 6.74 (1H, d, *J* 6.1), 7.41 (1H, t, *J* 9.3), 7.46 (1H, d, *J* 6.1), 7.55-7.60 (4H, m), 7.65 (1H, s), 7.70-7.73 (1H, m), 7.85 (1H, d, *J* 7.1); *m/z* (ES^+) 395 $[M+H]^+$.

EXAMPLE 5

4,2'-Difluoro-5'-(7-methyl-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl)-biphenyl-2-carbonitrile

A suspension of 3-bromo-8-methoxyimidazo[1,2-*a*]pyrazine (1.6 g, 7 mmol) in hydrogen bromide (30 wt % in acetic acid, 15 ml) was heated at 80°C for 90 min. The reaction was cooled, diluted with water (75 ml) then neutralised with solid sodium hydrogencarbonate. The resulting solid was collected by filtration, washed with water then dried under vacuum to afford 3-bromo-7*H*-imidazo[1,2-*a*]pyrazin-8-one as a white powder: δ_H (360 MHz, DMSO) 6.99 (1H, d, *J* 5.6), 7.29 (1H, d, *J* 5.6), 7.62 (1H, s). This powder was suspended in *N*,*N*-dimethylformamide (15 ml) then treated with sodium hydride (203 mg of a 60% dispersion in mineral oil, 8.4 mmol). The resulting mixture was heated at 60°C for 20 min then treated with iodomethane (870 µl, 14 mmol). After stirring for 15 min the reaction

was cooled, diluted cautiously with water (150 ml) and then extracted with dichloromethane (2 x 100 ml). The organics were combined, washed with water, dried over anhydrous magnesium sulphate, filtered and concentrated under high vacuum. The residue was triturated with diethyl ether and the resulting solid collected by filtration to furnish 3-bromo-7-methyl-7*H*-imidazo[1,2-*a*]pyrazin-8-one as a white solid (1.4 g, 88% over 2 steps): δ_H (360 MHz, DMSO) 3.45 (3H, s), 7.28 (1H, d, *J* 6), 7.39 (1H, d, *J* 5.6), 7.62 (1H, s).

A mixture of 3-bromo-7-methyl-7*H*-imidazo[1,2-*a*]pyrazin-8-one (171 mg, 0.75 mmol), 4,2′-difluoro-5′-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)biphenyl-2-carbonitrile (prepared as described in WO 02/074773) (392 mg, 1.2 mmol), palladium(II) acetate (7 mg, 0.03 mmol) and triphenylphosphine (8 mg, 0.03 mmol) in 1,4-dioxane (3 ml) and 2M aqueous sodium carbonate (0.75 ml) was heated at 80°C for 3 h. The reaction was cooled then diluted with ethyl acetate (25 ml). The mixture was extracted with 4N hydrochloric acid (25 ml) and the organics discarded. The aqueous was washed with ethyl acetate, filtered through GF/A glass microfibre filter paper and the filtrate made basic with solid sodium hydrogencarbonate. The resulting solid was collected by filtration, triturated with water and dried under high vacuum to afford 4,2′-difluoro-5′-(7-methyl-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazin-3-yl)biphenyl-2-carbonitrile as a cream-coloured solid (175 mg, 64%): δ_H (500 MHz, DMSO) 3.47 (3H, s), 7.19 (1H, d, *J* 6.0), 7.57-7.61 (2H, m), 7.72 (1H, s), 7.76-7.86 (4H, m), 8.08 (1H, dd, *J* 9 and 3); *m/z* (ES^+) 363 $[M+H]^+$.